Concise Review: The Promise of Human Induced Pluripotent Stem Cell-Based Studies of Schizophrenia

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ABSTRACT

Schizophrenia (SCZD) is a heritable developmental disorder. Although the molecular mechanism of disease remains unclear, insights into the disorder have been made through a vast array of experimental techniques. Together, magnetic resonance brain imaging, pharmacological, and post-mortem pathological studies have observed decreased brain volume, aberrant neurotransmitter signaling, reduced dendritic arborization, and impaired myelination in SCZD. Genome-wide association studies (GWAS) have identified common single nucleotide polymorphisms as well as rare copy number variants that contribute to SCZD, while mouse models of candidate SCZD genes show behavioral abnormalities and anatomical perturbations consistent with human disease. The advent of human induced pluripotent stem cells (hiPSCs) makes it possible to study SCZD using live human neurons with a genetic predisposition toward SCZD, even without knowledge of the genes interacting to produce the disease state. SCZD hiPSC neurons show cellular defects comparable to those identified in post-mortem human and mouse studies, and gene expression changes are consistent with predictions made by GWAS. SCZD hiPSC neurons represent a new tool to look beyond phenotype and begin to dissect the molecular mechanisms of SCZD.

INTRODUCTION

Schizophrenia (SCZD) is a neurological disorder characterized by three severe classes of symptoms: positive (hallucinations and delusions), negative (inability to speak, express emotion, or find pleasure), and cognitive (deficits in attention, memory, and planning) [1, 2]. The current treatment regimen for SCZD involves chronic treatment with powerful antipsychotics, the strong unpleasant side effects of which often result in cessation of treatment [1]. The life expectancy of patients with SCZD is up to 10 years less than the general population [3]; 40% of schizophrenics suffer from substance abuse [4], 20% are homeless [5], and 10% ultimately commit suicide [6, 7]. It is estimated that 1.1% of the global population over 18 years of age has SCZD, including 3 million Americans [1].

Human studies of SCZD have relied primarily on brain imaging, pharmacology, post-mortem pathology, and genetic studies of patient lymphocytes. Animal studies are limited in two important ways: (a) they do not reflect the complex genetic interactions that result in the vast majority of cases of SCZD, and (b) it is difficult to evaluate classic symptoms of SCZD such as hallucinations, delusions, and disorganized speech in mice. Although many insights have been made through these methods, the molecular and cellular defects that contribute to disease initiation and progression in neurons remain unknown. Recently, a third approach has been described to study SCZD [8, 9]. Reprogramming of patient fibroblasts to human induced pluripotent stem cells (hiPSCs), followed by hiPSC differentiation to neurons, produces a near limitless source of live human neurons, genetically identical to those present in patients, with which this disorder can be studied. This review will summarize the major findings of human and mouse studies of SCZD and compare these to early reports of SCZD hiPSC neurons.

INSIGHTS FROM HUMAN STUDIES

Human studies to date have used three major approaches: brain imaging, post-mortem pathology, and genome-wide association studies (GWAS).

Observations from Brain Imaging

Magnetic resonance imaging (MRI) can be used to estimate the volume of various brain regions, although these studies must be interpreted in the context of the high variability of brain measures across individuals [10]. Although group-average differences exist between SCZD patients and controls, anatomic MRI differences are not adequate for diagnosis. For analogy, although men tend to be taller than women on average, height is not sufficient to determine sex; male/female height differences are twice as predictive of gender as most MRI neuroimaging experiments are predictive of a diagnosis of SCZD.

In first-episode patients with SCZD, MRI studies consistently observe decreased whole brain volume (and increased...
ventricular volume) [12–14]. Specifically, the greatest decreases are observed in the gray matter of the hippocampus, basal ganglia, and thalamus (Fig. 1) [14–16]. In chronically ill patients, the volume loss is most pronounced in the frontal and temporal gray matter areas of the cortex [17], but whether these changes result from disease or long-term treatment with antipsychotic medications is unclear. Longitudinal studies have observed progressive decrease in brain volume and increase in lateral ventricle volume for at least 20 years after the onset of symptoms.

White matter is produced when oligodendrocytes wrap axons in sheaths of myelin, which increases the speed of neurotransmission as well as the timing and synchrony of neuronal firing patterns [18]. Beyond the well-characterized changes in gray matter, some studies also identify changes in the white matter of the brain in SCZD, particularly in the prefrontal and temporal lobes and corpus callosum [19]. Longitudinal brain imaging studies of childhood onset cases of SCZD have observed both progressive loss of cortical gray matter during adolescence and delayed white matter development [11].

Changes in blood flow and blood oxygenation in the brain are closely linked to neural activity. Functional MRI (fMRI) measures the change in blood flow as an indicator of brain activity, and fMRI comparisons of control and SCZD patients have revealed brain activity changes in the dorsolateral prefrontal cortex. At rest, SCZD patients show cortical hyperactivity and hyperconnectivity between the cortex and hippocampus [20] while during working memory tasks, SCZD patients show reduced activation of the cortex [21]. The molecular mechanism of these changes has not been explained.

Although brain imaging has associated clinical symptoms to the general brain areas affected, the relationship between brain imaging, cellular pathology, and the molecular mechanism of SCZD remains unknown.

Observations from Pharmacological Studies
The accidental discovery that Chlorpromazine (Thorazine) reduces psychotic symptoms, likely by functioning as an antagonist of dopamine (DA) receptors, provided the basis for the “DA hypothesis” of SCZD. This hypothesis proposed that excessive activation of D2 receptors was the cause of (the positive symptoms of) SCZD. By positron emission tomography (PET) imaging, researchers determine where given biological molecules, such as DA, bind in the brain. Such work has correlated DA receptor levels with the positive symptoms of SCZD (psychosis and delusions) [22], and strong evidence now links SCZD with increased DA synthesis, DA release, and resting-state synaptic DA concentrations [23]. Further support of this hypothesis is the psychosis-inducing effects of DA receptor agonists such as amphetamine.

The DA hypothesis is now believed to be overly simplistic. Among the DA antagonists, Clozapine is uniquely effective for treatment-resistant SCZD [24]. This ability may occur through a DA-independent mechanism, a hypothesis supported by anecdotal evidence that Clozapine effectively treats the psychotic symptoms associated with Parkinson’s disease (PD) without exacerbating the tremors, rigidity, and bradykinesia caused by the loss of DA neurons in PD [25]. Clozapine is an antagonist of D1, D2, D3, and D4 DA receptors, 5-HT2 receptors, 5-hydroxytryptamine (5-HT) receptors, H1 histamine receptor, and M1, M2, M3, and M5 receptors; an agonist of the M4 muscarinic receptor [26]; a modulator of glutamatergic neurotransmission [27]; and an inhibitor of GABAA receptor neurotransmission [28]; its complex pharmacological properties hint at the roles of other neuronal cell types in SCZD.

Glutamate (GLU)-blocking drugs such as ketamine induce many of the symptoms, including hallucinations and cognitive deficits, associated with SCZD [29], whereas the GLU receptor (GLUR2/3) agonist LY2140023 has been shown to ameliorate the symptoms of SCZD in recent clinical trials by Eli...
Lilly [30] (Fig. 2). The authors suggest that LY2140023 may work by reducing the presynaptic release of GLU at limbic synapses where these receptors are expressed. In summary, pharmacology of SCZD is intricate but evidence supports a role for altered DA and GLU neurotransmitter activity.

**Observations from Postmortem Studies**

Although brain imaging identified decreased brain volume in SCZD, post-mortem studies of brains from patients with SCZD have revealed no widespread neuronal loss or even a glial response to a potential neuronal injury. Instead, pathological studies have observed three major changes in SCZD brain tissue: increased density of pyramidal neurons, aberrations in interneurons, and decreased oligodendrocytes.

In the cortex, pathological changes are consistent with decreased neuronal connectivity in SCZD. Post-mortem studies have observed an increased density of cortical pyramidal neurons without changes in cell number [31, 32]. Neuronal soma are smaller [32], dendrites are shorter with reduced arborizations [33], and there is reduced dendritic spine density [34, 35]. The disturbances in prefrontal cognitive functioning in SCZD may be mediated by a process which involves atrophy of neuronal processes or synapses but stops short of actual neuronal loss [31].

Changes in RNA and protein levels of a number of key genes involved in neurotransmission have been observed in post-mortem SCZD brain tissue. GLUR expression is altered in SCZD; expression is decreased in the hippocampus and increased in the cortex [36]. Specifically in GABAergic interneurons, one finds decreased GAD67 and calcium-binding proteins in parvalbumin- and calbindin-positive GABAergic neurons. Changes in parvalbumin-positive GABAergic neurons are particularly relevant as they are thought to produce gamma oscillations, which synchronize pyramidal neuron firing, an activity that is impaired in SCZD. It is unclear whether decreased GABAergic inhibitory activity is a cell-autonomous cause of SCZD or if it results from decreased glutamatergic input on GABAergic inhibitory neurons in the disease state.

Finally, a number of studies have observed both fewer oligodendrocytes and decreased expression of myelin genes in post-mortem SCZD brains. This finding may be consistent with decreases in white matter observed in SCZD.

**GWAS of SCZD**

A complex genetic psychiatric disorder, SCZD has a large inherited component with an estimated heritability of 80–85% [37, 38]. With tens of thousands of SCZD patients genotyped to date, it is now widely accepted that the complicated heritability of SCZD results from polygenic inheritance of a combination of inherited common polymorphisms and both inherited and de novo rare copy number variations (CNVs). Because a large number of markers collectively account for risk of SCZD, the risk of each one is so small that it can be difficult to detect by GWAS. To date, most of the heritable variance of SCZD remains unaccounted for.

Early genetic studies of SCZD focused on traditional pedigree analyses. In a family identified in northern Scotland, more than half of the members suffer from mental illness, generally SCZD, and it was found that a balanced chromosomal translocation (1:11) segregated with disease. The disrupted gene on chromosome 1 was subsequently termed Disrupted-in-Schizophrenia-1 (DISC1) [39]. The genetic association between Neuregulin-1 (NRG1) and SCZD was first identified in association studies of Icelandic families [40] and subsequently confirmed in follow-up studies in multiple populations in Scotland, Ireland, Netherlands, Taiwan, Korea, and China [41–47]. Mutations in DISC1 are much more penetrant that those in NRG1 but are also exceedingly rare. Although studies of post-mortem brain tissue have consistently failed to detect alterations in DISC1 levels in typical SCZD patients, they do observe increased NRG1 in the hippocampus [48] and prefrontal cortex [49, 50] and decreased expression of its receptor ERBB4 [51–53], suggesting that NRG1 and ERBB4 may be affected even in the absence of detectable genetic lesions.

Common polygenic variation has been shown to contribute to SCZD. Studies of single nucleotide polymorphisms (SNPs) have estimated that thousands of alleles of very small effect account for nearly 30% of the genetic variance of SCZD [54–56]. Much of this common polygenic variation encompasses the major histocompatibility complex (MHC) region at 6p22-p21 that contains over 200 genes. Although MHC genes have been implicated in immune diseases such as type I diabetes, multiple sclerosis, Crohn’s disease, and rheumatoid arthritis, they also contribute to synaptic maturation [57–59]; therefore, this genetic evidence should not be presumed to be proof of immune abnormalities in SCZD.

Other common variants now well-implicated in SCZD include transcription factor 4 (TCF4) on chromosome 18q21, zinc finger protein 804A (ZNF804A) on 2q23.1, and neurogranin (NRGN) on 11q24.2 [55, 60]. TCF4 is a neuronal transcription factor essential for neurogenesis [61], and NRGN encodes a postsynaptic protein kinase substrate that binds calmodulin and is enriched in CA1 pyramidal neurons in the hippocampus [62], and ZNF804A is associated with altered neuronal connectivity in the dorsolateral prefrontal cortex [63]. CNVs are large deletions or duplications in the genome. So far, only rare (<1% of cases) and large CNVs (>100 kb) have been shown to confer high risk of SCZD. SCZD CNVs are highly penetrant and account for up to 20% of SCZD cases. CNVs identified to date disrupt genes, such as ERBB4 [64] or NRXN1 [65], or regions, including 1q21.1, 15q11.2, 15q13.3, 16p11.2, 22q11.2 [64, 66–68]. By comparing the DNA of both parents to the SCZD patient (proband), it was shown that CNV mutations frequently occur de novo and are not inherited from either parent. Given that the CNV mutation rate far exceeds the rate for nucleotide substitutions [69] and that current CNV assays detect only the largest CNVs, constituting just 5% of total CNVs, researchers may be underestimating the contribution of CNVs to SCZD [70].

The genetic basis of SCZD does not necessarily conform to classical disease boundaries. Many CNVs that confer high risk of SCZD have been implicated in autism, mental retardation, and epilepsy, while many SNPs associated with SCZD are shared with bipolar disorder [64, 66–68]. It is likely that numerous disruptions in any number of key neurodevelopmental pathways may be sufficient to produce a diseased state that could ultimately manifest as SCZD.

**INSIGHTS FROM MOUSE MODELS**

Although causal mutations for SCZD have not been identified, several genetic mouse models of SCZD have been developed. Of these, mice with decreased activity of DISC1, NRG1, ERBB4, or the 22q11 genes show behavioral abnormalities and anatomical perturbations that may be relevant to SCZD.

**DISC1 Mice Recapitulate Aspects of the SCZD Phenotype**

DISC1-mutant animals demonstrate behavioral abnormalities such as decreased learning and memory [71–73], decreased sociability [71, 72], depression [71, 72], hyperactivity [72, 73], and aggression [72], which are consistent SCZD. Mice with
excitatory glutamatergic neurons. NRG1 increases the number, interneurons, while NRG1 is primarily localized at synapses in defects in these mice [83]. ERBB4 is enriched in GABAergic antipsychotic drug Clozapine reverses the behavioral and spine apical maturation and function [83, 86, 87]. Treatment with the synaptic plasticity, enhanced neurotransmitter release, altered calcium kinetics in CA3 presynaptic terminals, and impaired long-range synchrony between the hippocampus and prefrontal cortex [90–92].

Figure 3. Representative phenotypes present in dominant negative Disrupted-in-Schizophrenia-1 (DISC1) mouse models of SCZD. Top, increased ventricular volume in dnDISC1 mice. Middle, reduced dendritic arborization in dnDISC1 mice. Bottom, reduced frequency of spontaneous inhibitory postsynaptic currents in dnDISC1 mice. Adapted from Refs. [71] and [72]. Abbreviation: SCZD, schizophrenia

reduced DISC1 activity during development have reduced neurite outgrowth [74], reduced cortical migration [74], reduced dendritic complexity [71, 73], reduced hippocampal synaptic transmission [71, 73], and slightly enlarged ventricles [72] but no significant structural defects or signs of neurodegeneration (Fig. 3). Conversely downregulation of DISC1 in adulthood causes accelerated neural differentiation and increased neural excitability in newborn neurons [75]. DISC1 seems to function as a molecular scaffold; it interacts with multiple proteins, including the centrosomal protein NUDEL [74, 75] required for neurite outgrowth and neuronal migration [76, 77], as well as phosphodiesterase 4B [78], a key regulator of cyclic adenosine monophosphate (cAMP), linked to learning, memory, and mood [79–81]. It remains unknown which of these functions is responsible for SCZD pathogenesis.

NRG1 and ERBB4 Mice Demonstrate Role of Excitatory Glutamatergic Input onto GABAergic Inhibitory Neurons in SCZD

Although mice lacking both copies of either the NRG1 or ERBB4 genes are embryonically lethal due to cardiac defects, heterozygous null NRG1 and ERBB4 animals have behavioral abnormalities such as hyperactivity, increased aggression, and deficiencies in prepulse inhibition, a measure of sensory gating that is abnormal in SCZD [42, 82, 83]. Although cell layers in the cerebral cortex, hippocampus, and cerebellum develop normally in the mutant mice, there are defects in neurite outgrowth and arborization neuronal migration [84, 85] and impaired synaptic maturation and function [83, 86, 87]. Treatment with the antipsychotic drug Clozapine reverses the behavioral and spine defects in these mice [83]. ERBB4 is enriched in GABAergic interneurons, while NRG1 is primarily localized at synapses in excitatory glutamatergic neurons. NRG1 increases the number, size, and activity of excitatory synapses on GABAergic interneurons [88, 89], renewing support for the hypothesis that SCZD results, at least in part, due to reduced excitatory glutamatergic input onto GABAergic inhibitory neurons.

22q11 Models Impaired Long-Range Synchrony of Neural Activity

Mouse models of 22q11.2 represent the first studies of a CNV associated with SCZD; SCZD develops in about 20–25% of individuals with a chromosome 22q11.2 microdeletion. Mice with disruptions of 22q11.2 genes have fewer cortical neurons with slightly smaller spines, altered short- and long-term synaptic plasticity, enhanced neurotransmitter release, altered calcium kinetics in CA3 presynaptic terminals, and impaired long-range synchrony between the hippocampus and prefrontal cortex [90–92].

Olfactory neural precursors (ONPs) can be expanded following exfoliation of the nasal cavity via a noninvasive method [93]. ONPs are capable of self-renewal as well as differentiation to mature electrophysiologically active neurons. ONPs from SCZD patients and controls have been generated and banked [93] to ask whether genetic, structural, and/or functional abnormalities are present in SCZD neurons. By similar methods, a second group generated ONPs from control and SCZD patients and performed gene expression comparisons, which identified differences in neurodevelopmental pathways associated with cell migration and axon guidance [94].

ONPs are one source of live human neurons for the study of SCZD. Although differences between SCZD and control ONPs have been identified, it is unclear whether SCZD ONPs will recapitulate all of the neuronal defects present in brain regions such as the cortex or hippocampus. Additionally, ONPs cannot yet be used as a source of cells from the neural lineages specifically implicated in SCZD: glutamatergic neurons, GABAergic neurons, dopaminergic neurons, and oligodendrocytes.

Chiang et al. [9] first published the generation of hiPSCs from SCZD patients with a DISC1 mutation but did not characterize neurons differentiated from these hiPSCs. We then demonstrated that SCZD hiPSC neurons had defects in neuronal connectivity and gene expression, which could be ameliorated following treatment with the antipsychotic Loxapine [8]. Specifically, we observed reduced neuronal connectivity, reduced outgrowths from soma, and reduced postsynaptic density protein 95 (PSD95) dendritic protein levels, all of which are cellular phenotypes previously described in post-mortem SCZD brain tissue as well as animal models of SCZD (Fig. 4). Additionally, we observed gene expression differences in SCZD neurons relative to controls, 25% of which had been previously implicated in SCZD, with significant perturbations in genes associated with the WNT pathway, cAMP signaling, and GLU receptor expression. We hypothesize that studies of SCZD hiPSC neurons from an increased number of patients might identify core pathways of genes contributing to SCZD. Pedrosa et al. have also generated SCZD hiPSCs from three patients and report that SCZD
hiPSC neurons express a number of transcription factors, chromatin remodeling proteins, and synaptic proteins relevant toSZCD pathogenesis, independently validating the potential utility of hiPSC neurons in modeling SCZD [95].

Although hiPSC-based studies show exciting promise for the study of SCZD, they remain limited by three types of variabilities: neuron-to-neuron, hiPSC-to-hiPSC, and patient-to-patient. Interneuron variability is countered by studying more homogeneous populations of hiPSC neurons, generated by direct differentiation protocols to specific neuronal subtypes and subsequent purification by fluorescence-activated cell sorting (FACS). Inter-hiPSC variation is addressed by comparing multiple hiPSC lines per patient, particularly as it is well-established that genetic and epigenetic differences exist between hiPSC lines. Finally, interpatient variability can be tackled by studying an increased number of patients and controls, and particularly by selecting homogeneous patient cohorts characterized by common clinical endophenotypes, pharmacological responses, or genetic mutations. Using hiPSC neurons, researchers can now begin to dissect the molecular mechanism of pharmacological response and screen for new drugs to improve cellular phenotypes in SCZD neurons from patients with clear clinical pharmacological nonresponsiveness.

**MOVING FORWARD: FUTURE hiPSC STUDIES OF SCZD**

Brain-imaging studies have identified structural changes in SCZD brains but cannot resolve which neuronal cell types are affected in SCZD. Pharmacological studies have identified a role for DA and GLU; however, chronic antipsychotic treatment alters brain structure and neural activity, confounding studies of human patients affected with SCZD. GWAS studies have yet to account for most of the heritable variance of SCZD. Although animal models have recapitulated aspects of the behavioral and cellular phenotypes of SCZD, they lack the ability to define the complex interacting genetic factors that contribute to disease. hiPSC-based studies will comple-

ment brain imaging, pathological, pharmacological, genetic, and animal studies of SCZD.

It will be critical that researchers carefully consider which specific subtypes of neurons should be compared using hiPSC neurons studies. We propose that the field begin to characterize cell-autonomous defects in midbrain DA (mDA) and cortical glutamatergic (cGLU) and GABAergic SCZD hiPSC neurons.

An efficient protocol can now differentiate pluripotent stem cells to populations consisting of approximately 20% DA neurons [96] by recapitulating developmental cues found in the ventral midline when SHH, FGF8, and WNT1 initiate DA differentiation; immature mDA neurons express NURR1, EN1/2, and LMX1A/B, whereas mature mDA neurons also express tyrosine hydroxylase and aromatic l-amino acid decarboxylase [97]. Studies using mouse ESCs have shown that NODAL antagonists (LEFTYA) induce expression of the forebrain marker brain-factor 1 (BF1, FOXG1) and subsequent treatment with WNT antagonists causes regional specification toward cortical fate [98]. Genes such as EMX1, FEZF2, and FEZ are expressed in immature cGLU neurons [99–101], while mature cGLU neurons express CTIP2 and OTX1 [99, 102, 103]. Subsequent culture with FGF2 has been shown to increase GABAergic differentiation [104]; GABA neurons can be identified by expression of key GABAergic markers, such as glutamate decarboxylase (GAD65/67), DARPP32, ARPP21, CALBINDIN, or CALRETININ [105], although few if any regional markers of basal ganglia identity have been identified.

Future molecular studies of hiPSC neurons should incorporate SNP, CNV, and gene expression data. Studies of quantitative trait loci (eQTLs) will determine how genetic lesions affect gene expression in SCZD neurons. Current eQTL studies can only compare a limited supply of heterogeneous postmortem brain tissue confounded by variables such as patient treatment history, drug/alcohol abuse, and poverty. Ideally, hiPSC-based eQTL studies would produce a renewable supply of more homogeneous cell populations. As hiPSC generation, neuronal differentiation and subtype purification are streamlined and made more efficient, it will become possible to generate any defined neuronal subtypes from hiPSCs generated from hundreds of patients with known genetic backgrounds.
It is now time to begin to synthesize the disparate fields of brain imaging, neurobiology, and genetics. By generating hiPSC neurons from more and better-characterized patient cohorts, one can now test whether the severity of clinical outcome is predictive of the magnitude of cellular phenotype, if genetic lesions correlate to neuronal gene expression differences or if clinical pharmacological response is predictable by hiPSC neuronal drug response. Beyond correlating genetic lesions to the disease state, we can assay the expression or activity of genes identified through GWAS, both in the specific patient in whom the lesion was identified and across cohorts of SCZD patients. By carefully selecting from patients with well-characterized diagnosis, MRI brain scans, genotyping data, and clinical treatment history, hiPSCs can be generated specifically from SCZD patients with extreme endophenotypes, for example, patients showing drastically altered brain volumes by MRI or clear treatment resistance. Neurons derived from these patients will allow testing of the genetic causes of each endophenotype. With hiPSCs, we can finally move beyond phenotyping of SCZD patients and begin to develop well-controlled experiments to test the specific molecular and cellular effects of disease and pharmacological treatment and response. It is time to begin correlating clinical, genetic, and pharmacological studies in vitro.

CONCLUSION

It is now time to begin to synthesize the disparate fields of brain imaging, neurobiology, and genetics. By generating hiPSC neurons from more and better-characterized patient
cohorts, one can now test whether the severity of clinical outcome is predictive of the magnitude of cellular phenotype, if genetic lesions correlate to neuronal gene expression differences or if clinical pharmacological response is predictable by hiPSC neuronal drug response. Beyond correlating genetic lesions to the disease state, we can assay the expression or activity of genes identified through GWAS, both in the specific patient in whom the lesion was identified and across cohorts of SCZD patients. By carefully selecting from patients with well-characterized diagnosis, MRI brain scans, genotyping data, and clinical treatment history, hiPSCs can be generated specifically from SCZD patients with extreme endophenotypes, for example, patients showing drastically altered brain volumes by MRI or clear treatment resistance. Neurons derived from these patients will allow testing of the genetic causes of each endophenotype. With hiPSCs, we can finally move beyond phenotyping of SCZD patients and begin to develop well-controlled experiments to test the specific molecular and cellular effects of disease and pharmacological treatment and response. It is time to begin correlating clinical, genetic, and pharmacological studies in vitro.

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